UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION
OFFICE OF PESTICIDE PROGRAMS REGISTRATION DIVISION (7505P)

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DOCUMENT CONTAINS CONFIDENTIAL BUSINESS INFORMATION

DP BARCODE No.: D456102; **FILE SYMBOL/REG. No.**: 11603-LI; **PRODUCT NAME**: Quizalofop-P-Ethyl Technical; **DECISION No.**: 558492; **PC Code(s)**: 128709; **ACTION CODE**: R334; **FOOD Use**: Yes

DATE: November 17, 2020

SUBJECT: Product Chemistry Review of "Quizalofop-P-Ethyl Technical"

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REGISTRANT: ADAMA Agan, Ltd.

MRID Numbers: 51008201, 51008202, 51008203, 51008204, 51008205, 51008206, 51008207

INTRODUCTION:

On behalf of the registrant, Makhteshim Agan of North America, Inc. (d/b/a ADAMA) has submitted an application to register the new technical-grade product "Quizalofop-P-Ethyl Technical" which is substantially similar in composition and labeling to the product "Quizlofop-P-Ethyl MUP Herbicide" (EPA Reg. No. 33906-10). In support of the application, the registrant submitted Group A product chemistry data with MRID Nos. 51008201 and 51008202, and Group B product chemistry data with MRID Nos. 51008203 through 51008207. The CSF (dated 12/18/2019) for the basic formulation was also submitted for the product. CITAB has been asked to determine the acceptability of the product chemistry data and proposed Basic CSF.

The data package was first reviewed by Summitec Corporation.

SUMMARY OF FINDINGS:

1. Group A guidelines:

830.1550: (product identity & composition)

The active ingredient (R isomer of Quizalofop-P-Ethyl) was adequately described (MRID No. 51008201). The nominal concentration of the active ingredient (95.7%, from the proposed Basic CSF dated 12/18/2019) is the same as the average derived from the five-batch preliminary analysis results (95.67%, refer to Page 54 of 247 in the Confidential Attachment of MRID No. 51008202). The content of the active ingredient given on the proposed Basic CSF matches that stated on the product label.

The product chemistry data submitted for Guideline 830.1550 satisfy the data requirements of 40 CFR §158.320.

830.1600: (description of materials used to produce the product)

Safety Data Sheets (SDSs) of all the starting materials, and their suppliers and specifications were provided in MRID No. 51008201. The product chemistry data submitted for Guideline 830.1600 satisfy the data requirements of 40 CFR §158.325.

830.1620 (description of production process)

A description of the production process, chemical pathways, flow charts, and quality control measures were provided in MRID No. 51008201. The product chemistry data submitted for Guideline 830.1620 satisfy the data requirements of 40 CFR §158.330.

830.1670 (discussion on the formation of impurities)

Potential impurities were identified and quantified as part of the five-batch preliminary analysis (MRID No. 51008202). [redacted] impurities were found to be present at average concentrations ≥ 0.1% w/w. The formation of the impurities was fully discussed (MRID No. 51008201). There is one impurity of toxicological significance in Quizalofop-P-Ethyl Technical. It was found to be present at an average level below the limit permitted by European Food Safety Authority (EFSA).

The product chemistry data submitted for Guideline 830.1670 satisfy the data requirements of 40 CFR §158.340.

830.1700 (preliminary analysis)

The five-batch preliminary analysis of Quizalofop-P-Ethyl Technical was conducted by ADAMA Agan, Ltd. (Analytical Laboratory, Northern Industrial Zone, Ha'Ashlag St., Ashdod, 7752009, Israel). The content of the active ingredient was determined using HPLC-UV with external standard calibration which was validated with respect to specificity, linearity and precision (MRID No. 51008202). The concentrations of the active ingredient in the five batches were: 95.78, 95.64, 95.79, 95.47 and 95.68% (average 95.67%, from Page 54 of 247 in the Confidential Attachment of MRID No. 51008202). Certificates of analysis for all five batches were provided in MRID No. 51008202.

The product chemistry data submitted for Guideline 830.1700 satisfy the data requirements of 40 CFR §158.345.

830.1750 (certified limits)

The registrant proposed certified limits for the active ingredient with a narrower range than one EPA standard allows. The upper certified limits for the impurities were proposed with wider ranges to allow for manufacturing variability. The sufficient justifications were provided. The nominal concentrations of the active ingredient and identified impurities listed on the proposed Basic CSF are the same as their respective averages derived from the five-batch preliminary analysis results.

The product chemistry data submitted for Guideline 830.1750 satisfy the data requirements of 40 CFR §158.350.

830.1800 (enforcement analytical method)

The active ingredient (R isomers of Quizalofop-P-Ethyl) in Quizalofop-P-Ethyl Technical was quantified by a two-step analytical method involving HPLC-UV with external standard calibration, which was validated in terms of specificity, linearity, and precision, but not for accuracy (MRID No. 51008202). The active ingredient was identified by using HPLC-MS and HPLC-UV respectively against Quizalofop-P-Ethyl analytical standard (MRID No. 51008202).

The analytical methods used to determine the amounts of the impurities were provided in MRID No. 51008202 (refer to "830.1700 (preliminary analysis)" under section "Confidential Attachment" for a summary of the methods).

The product chemistry data submitted for Guideline 830.1800 do not satisfy the data requirements of 40 CFR §158.355.

2. Group B guidelines (physical-chemical properties):

Adequate data were submitted for color, physical state, odor, stability to normal/elevated temperatures, corrosion characteristics, pH, melting point, boiling point, UV/Visible absorption, density, dissociation constants in water, partition coefficient, water solubility and vapor pressure (MRID Nos. 51008203 through 51008207). Waivers were requested for stability to metals/metal ions, oxidation/reduction, flammability, explodability, and they will be evaluated by the Agency. No data were provided for miscibility and viscosity as they are irrelevant to the product.

A 14-day accelerated storage stability study was conducted on Quizalofop-P-Ethyl Technical (Batch No. 1163) at 54 ± 2°C (MRID No. 51008203). The test substance was stored in a polyethylene commercial bag. The concentration of the active ingredient was determined by using a two-step analytical method involving HPLC-UV which was validated for specificity, linearity and precision. Also, the test substance was visually examined for any physical appearance changes (color, physical state and odor). The results showed that the test substance was stable for 14 days at 54 ± 2°C. The average concentrations of the active ingredient after 0 and 14 days of storage were respectively 95.57% and 95.51% w/w, which are within its certified limits listed on the proposed Basic CSF (dated 12/18/2019). Additionally, no changes in the physical appearance of the test substance were noted.

The 14-day corrosion characteristics study was performed concurrently with the storage stability study at 54 ± 2°C (MRID No. 51008203). The test substance (Batch No. 1163) was stored in the commercial packaging (polyethylene). The results showed that no signs of deterioration or distortion were noted on the packaging during the course of the study. Also, there were no weight changes in the packaging.

CONCLUSIONS:

The CITAB has reviewed the proposed Basic CSF and the supporting group A and group B data for Quizalofop-P-Ethyl Technical and has concluded that:

1. The data submitted for the Group A guidelines are acceptable.

2. The data submitted for the Group B guidelines and waiver requests are acceptable.

3. The impurities listed on the CSF are [redacted]

4. The proposed Basic CSF (dated 12/18/2019) is acceptable and supported by the five-batch preliminary analysis data.

5. The product is not similar to the cited CSF of product Reg. No. 33906-10 dated 3/17/1999 in term of AI's nominal concentration, impurity profiles and physical and chemical properties.

6. The content of the active ingredient given on the proposed Basic CSF matches that stated on the product label. There is no new recommendation.

830.1550. Product identity & composition: (MRID No. 51008201)

Common Name: Quizalofop-P-Ethyl (R isomer)

IUPAC Name: Ethyl (R)-2-[4-(6-chloroquinoxalin-2-yloxy) phenoxy]propionate

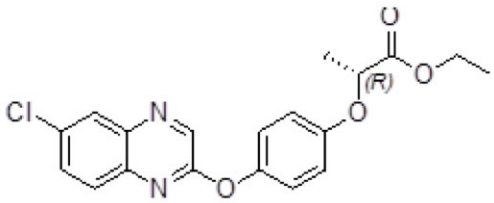
CAS Name: 2-[4-[(6-Chloro-2-quinoxalinyl)oxy]phenoxy] propanoic acid ethyl ester (R isomer)

CAS Number: 100646-51-3

Molecular formula: $C_{19}H_{17}ClN_2O_4$

Molecular weight: 372.8 g/mol

Structural formula:



Group A Product Chemistry Data

Table 1. Manufacturing and Impurity Data for "Quizalofop-P-Ethyl Technical"				
GLN	Requirement	MRID	Status	Details and /or Deficiency
830.1550	Product Identity and composition	51008201	A	Adequately described
830.1600	Description of materials used to produce the product	51008201	A	SDSs of the starting materials, and their suppliers and specifications were provided.
830.1620	Description of production process	51008201	A	A detailed description of the production process was provided.
830.1670	Discussion of formation of impurities	51008201	A	The identities and origins of potential impurities were provided.
830.1700	Preliminary analysis	51008202	A	A five-batch analysis of the active ingredient and impurities was provided.
830.1750	Certified limits	51008201	A	Sufficient justifications were provided for the expanded certified limits for the active ingredient and impurities.
830.1800	Enforcement analytical method	51008202	A	The analytical method for quantifying the active ingredient was not validated for accuracy.
A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress; U = Up-grade (additional information required);				

830 Series Subgroup B (Physical-Chemical Properties)

Table 2: Physical and Chemical Properties for "Quizalofop-P-Ethyl Technical"				
GLN	Requirement	MRID	Status	Result or Deficiency
830.6302	Color	51008203	A	Orange to brown
830.6303	Physical state	51008203	A	Solid
830.6304	Odor	51008203	A	Slight odor
830.6313 830.6317	Stability to normal and elevated temperatures, metals, and metal ions	51008203, 51008207	A	The product was found to be stable when stored at 54 ± 2°C for 14 days. It is not expected to come into contact with metals and metal ions during storage.
830.6314	Oxidation/reduction: chemical incompatibility	51008204	Waiver requested	
830.6315	Flammability	51008204	Waiver requested	
830.6316	Explodability	51008204	Waiver requested	
830.6317	One Year storage stability	51008203	A	The product was found to be stable when stored in the polyethylene commercial packaging at 54 ± 2°C for 14 days.
830.6319	Miscibility		N/A	The product is a solid.
830.6320	One Year corrosion characteristics	51008203	A	No signs of corrosion were noted on the polyethylene commercial packaging during the 14-day storage stability study at 54 ± 2°C.
830.7000	pH	51008203	A	6.3 (1% w/w aqueous dispersion)

Table 2: Physical and Chemical Properties for "Quizalofop-P-Ethyl Technical"

GLN	Requirement	MRID	Status	Result or Deficiency
830.7050	UV/Visible absorption	51008204	A	See nested table below
830.7100	Viscosity		N/A	The product is a solid.
830.7200	Melting point	51008205	A	76.4 ± 0.1°C
830.7220	Boiling point	51008205	A	The product did not boil between 25°C and 400°C under 99.7 kPa.
830.7300	Density	51008206	A	1.361 g/mL at 20.0 ± 0.1°C
830.7370	Dissociation constants in water (DC)	51008207	A	The pKa value was not determined as the product did not dissociate.
830.7550	Partition coefficient	51008207	A	Log Pow = 4.61
830.7840	Water solubility	51008207	A	0.61 mg/L
830.7950	Vapor pressure	51008207	A	1.1×10^{-4} mPa at 20°C

Condition	λ_{max} (nm)	ε (L/mol.cm)
Neutral	234	31355
	271	6599
	333	6300
Acidic	235	28649
	240 shoulder	27603
	273 shoulder	5527
	334	5645
Basic	234	28940
	241 shoulder	27948
	273 shoulder	5289
	334	5631
	343 shoulder	4415

A = Acceptable; N = unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress; U = Up-grade (additional information required); W = waivers

830.1800 (enforcement analytical method)
(MRID Nos. 51008201 and 51008202)

The active ingredient in Quizalofop-P-Ethyl Technical is the optical isomer R of Quizalofop-P-Ethyl. It was quantified by a two-step method. In the first step, the total amount of R and S isomers was determined by using HPLC-UV at 254 nm with external standard calibration, which was validated with respect to specificity, linearity, and precision (repeatability and reproducibility), but not for accuracy (MRID Nos. 51008201 and 51008202). With this method, the two isomers could not be separated and eluted as one chromatographic peak. In the second step, the ratio of the two isomers was determined by HPLC using peak area normalization method, thus allowing for quantification of each isomer (refer to section "830.1750 (preliminary analysis)" below for the detailed method of analysis of the S isomer). The Quizalofop-P-Ethyl analyte (containing both isomers) was identified based on retention time and spectral matching by using HPLC-UV and HPLC-MS respectively against Quizalofop-P-Ethyl analytical standard (MRID No. 51008202).

The samples of Quizalofop-P-Ethyl Technical were dissolved in acetonitrile, and then separated by a HPLC system using the following chromatographic conditions. The details for sample preparation were provided in the Confidential Attachment of MRID No. 51008202, p. 21 of 247. The retention time for Quizalofop-P-Ethyl was approximately 10 minutes.

Instrument: Shimadzu HPLC system equipped with UV detector, automatic injector, and Class-VP chromatographic data system software.

Column: UniverSil C18 5μm, 250 x 4.6 mm ID

Mobile phase:	Gradient
Detector:	254 nm
Injection volume:	10 μl
Flow rate:	2.0 mL/min
Temperature:	ambient

Gradient:

Time (min)	% Acetonitrile	% Acidified water
0	60	40
15	60	40
18	80	20
23	80	20
26	60	40
29	60	40

With the linear calibration curve, the total content of R isomer and S isomer of Quizalofop-P-Ethyl (% w/w) was calculated by using the formula below.

% Quizalofop-P-Ethyl (R and S isomers)

$= \{[(\text{Response}_{\text{Sample}} \times \text{Slope}) + \text{Intercept}] / \text{Concentration}_{\text{Sample}}\} \times 100$

Where:

$\text{Response}_{\text{Sample}}$ = Response of Quizalofop-P-Ethyl in sample solution

Concentration $_{Sample}$ = Concentration of sample solution (mg/L)

In the second step of the enforcement analytical method, the optical purity for the R isomer or S isomer was calculated by using the area percent method:

% R isomer = (Area $_{R\ isomer}$ x 100) / (Area $_{S\ isomer}$ + Area $_{R\ isomer}$)

% S isomer = (Area $_{S\ isomer}$ x 100) / (Area $_{S\ isomer}$ + Area $_{R\ isomer}$)

Calculation of the active ingredient (R isomer of Quizalofop-P-ethyl) content in Quizalofop-P-ethyl technical was performed according to the following equation:

Active Ingredient (% w/w) = [% R isomer x % Quizalofop-P-Ethyl (R and S isomers)] / 100

A summary of the method validation data for quantifying Quizalofop-P-Ethyl (containing both R and S isomers) is presented in the table below.

Components		**Results**[a]
Specificity		[redacted]
Linearity of response	Correlation Coefficient	
	Range of Linearity	
Precision (% RSD)	Repeatability	
	Reproducibility	
Accuracy (% Recovery)		

[a]Data are from the Confidential Attachment of MRID No. 51008202, pp. 35 – 37, 56 – 57 and 78 of 247.

Quality control process information may be entitled to confidential treatment

Pages 10-25*Manufacturing process information may be entitled to confidential treatment*

DATA EVALUATION RECORD

Quizalofop-P-Ethyl Technical

STUDY TYPE: PRODUCT CHEMISTRY REVIEW

OCSPP 830.1550; 830.1600; 830.1620; 830.1670; 830.1700; 830.1750; 830.1800; 830.6302; 830.6303; 830.6304; 830.6313; 830.6314; 830.6315; 830.6316; 830.6317; 830.6319; 830.6320; 830.7000; 830.7050, 830.7100; 830.7200, 830.7220, 830.7300; 830.7370; 830.7550; 830.7840; 830.7950

MRIDS 51008201, 51008202, 51008203, 51008204, 51008205, 51008206, 51008207

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Task Order No. Product Chem – 3-10b

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Pages 27-28*Confidential Statement of Formula may be entitled to confidential treatment*